Vasopressors, Steroids and Intravenous Fluids in Septic Shock

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Disclosures

No disclosures

Objectives

- Define sepsis
- List two scoring tools for the diagnosis of sepsis
- Define sepsis and septic shock
- Explain the basic pharmacology of vasopressor and inotropes in septic shock
- Choose the “best choice” first line vasopressor for the patient
- Identify two strategies for choosing the correct volume and solution for fluid resuscitation
- Understand how to apply the current guidelines and research in choosing the correct vasopressors, intravenous fluids and steroids for the patient in septic shock

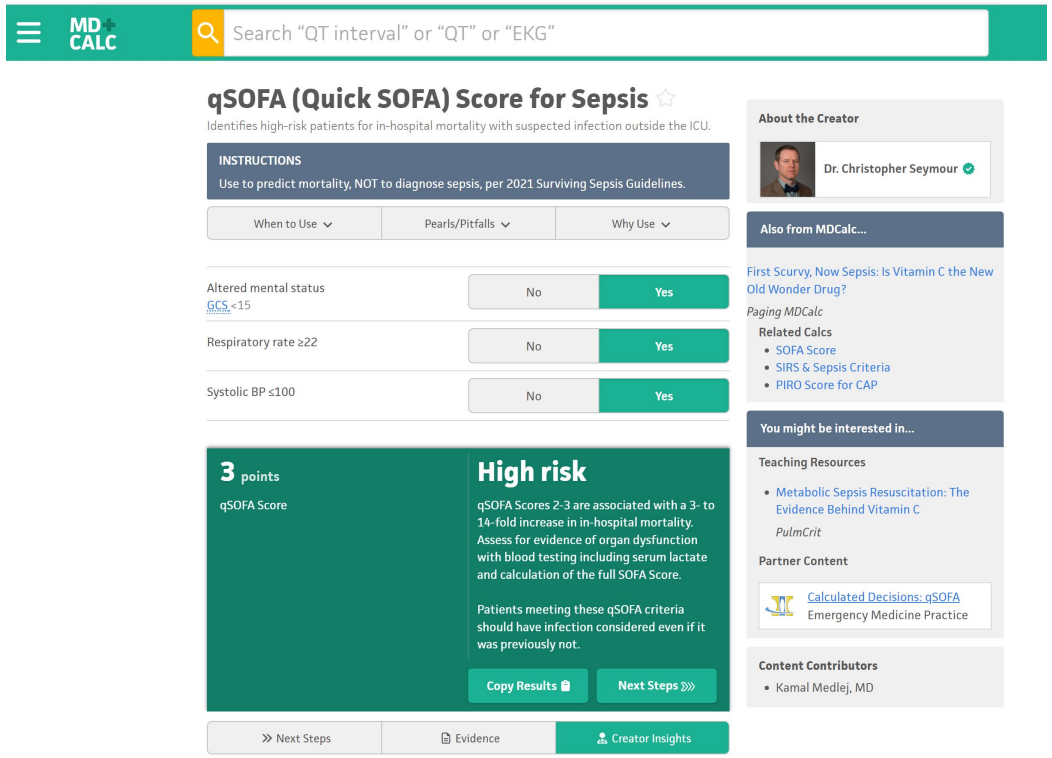
Sepsis-3 Definition

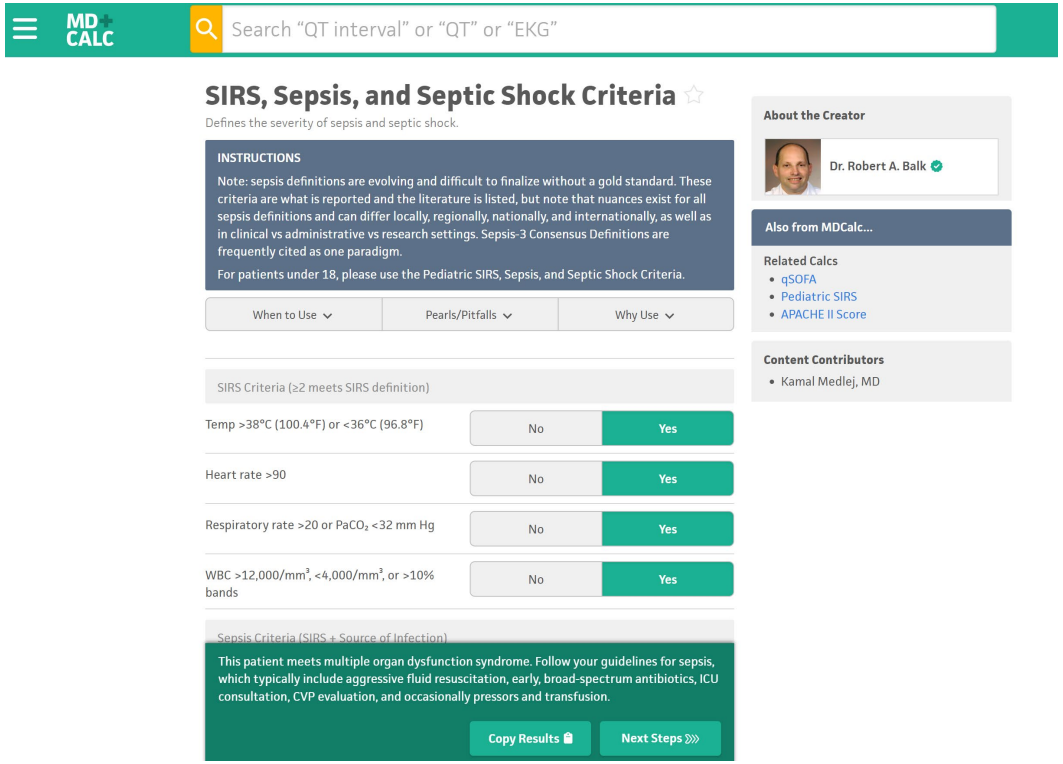
- Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection
- For clinical operationalization, organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10%

Sepsis-3 Definition of Septic Shock

- Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone
- Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/L in the absence of hypovolemia.
- This combination is associated with hospital mortality rates greater than 40%.

Sepsis Scoring Tools





SPECIAL ARTICLE

Executive Summary: Surviving Sepsis Campaign: International Guidelines for the Management of Sepsis and Septic Shock 2021

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The Surviving Sepsis Campaign (SSC) International Guidelines for the Management of Sepsis and Septic Shock provide guidance on the care of hospitalized adult patients with (or at risk for) sepsis, based on systematic summary and assessment of relevant literature. This executive summary reviews the history, scope, methodology, and major recommendations of the guidelines, focusing on aspects that are new or different compared with the 2016 guidelines that were published in 2017. Full description of the guidelines process and recommendations are provided in the complete guidelines document.

KEY WORDS: adults; evidence-based medicine; guidelines; sepsis; septic shock

HISTORY AND SCOPE OF THE GUIDELINES

The SSC first published guidelines for the management of severe sepsis and septic shock in 2004. Updates were published in 2008, 2012, and 2017. The guidelines are sponsored by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), with methodological support by the Guidelines in Intensive Care Development and Evaluation (GUIDE) group, and endorsement by 24 additional societies. There is no funding from any industry partner. Panel membership, patient involvement, and conflict of interest management are discussed in the complete guidelines document.

The guidelines provide recommendations on the management of sepsis, focusing on aspects of care specific to sepsis and limiting duplication with other guidelines wherever possible. It is not intended to replace clinical judgement, which must account for the unique circumstances of an individual patient. Following the recommendation of SCCM and ESICM, there are now separate guidelines for sepsis in children (1). The SSC also published separate guidelines specific to the management of COVID (2, 3).

The 2021 guidelines largely apply to high-resource settings but discuss applicability of the recommendations to lower-resource settings as data allow. The SSC

Vasopressors

Norepinephrine

- Levophed
- First line vasopressor in patients with septic shock
- Stimulates alpha adrenergic receptors and beta1 adrenergic receptors
- Alpha affinity >beta affinity

Dopamine

Not a preferred vasopressor for septic shock. May use for symptomatic bradycardia

Stimulates both adrenergic and dopaminergic receptors

May increase rate of tachyarrhythmias

Surviving Sepsis, 2021 Hemodynamic Management Guidelines

- For adults with septic shock, we recommend using norepinephrine as the first-line agent over other vasopressors
- For adults with septic shock on norepinephrine with inadequate mean arterial pressure levels, we suggest adding vasopressin instead of escalating the dose of norepinephrine
- For adults with septic shock and inadequate mean arterial pressure levels despite norepinephrine and vasopressin, we suggest adding epinephrine

Comparison of Dopamine and Norepinephrine in the Treatment of Shock (SOAP II Trial)

- Multicenter RCT published 2010, NEJM
- Compared first line use of dopamine versus norepinephrine in 1679 patients with shock
- Primary outcome was death at 28 days
- Secondary outcomes were number of days without organ support and adverse events
- Initial analysis showed no difference in rate of total deaths at 28 days, did show an increase in adverse events
- Most common adverse event was arrythmia (atrial fibrillation) and this occurred most frequently in the dopamine group.
- Subgroup analysis showed an increased rate of death in the subgroup with cardiogenic shock however not in the groups with septic or hypovolemic shock.

Dopamine Versus Norepinephrine in the Treatment of Septic Shock

- Published in Journal of Critical Care Medicine in 2012
- Meta analysis included five observational (1,360 patients) and six randomized (1,408 patients) trials, totaling 2,768 patients (1,474 who received norepinephrine and 1,294 who received dopamine)
- In patients with septic shock, dopamine administration was associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine administration

Vasopressin

- Vasostrict
- Second line vasopressor in septic shock
- Stimulates V1-V2
- May decrease or have a neutral effect on HR

Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock (VASST Trial)

- Multicenter, RCT, published in 2008, NEJM (778 adult patients)
- Compared the addition of vasopressin to patients in septic shock who were requiring a minimum of 5 mcg of norepinephrine to the addition of vasopressin (0.03) or norepinephrine (5-15 mcg/min) in addition to open label vasopressors
- Primary end point was 28-day mortality
- Findings: Low dose vasopressin did not reduce mortality rates as compared with norepinephrine in patients with septic shock who were treated with catecholamine vasopressors
- No significant difference at 28- or 90-day mortality and no significant difference in adverse events between the two groups.
- There was a 5.7% absolute mortality reduction in the vasopressin group which didn't reach statistical significance. This improvement was restricted to the prospectively defined group of patients with less severe septic shock (defined as initial norepinephrine requirement <15 mcg/min)

Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients with Septic Shock (VANISH Trial)

Multicenter, RCT, published in 2016, JAMA (409 adult patients)

Compared the effect of early vasopressin vs norepinephrine on Kidney failure in patients with septic shock

Primary outcome was kidney failure free days during the 28 day period after randomization

Rates of renal replacement therapy, mortality and serious adverse events were secondary outcomes

Findings did not improve the number of kidney failure free days

Epinephrine

Adrenalin

Third line vasopressor.

Consider use in septic shock, if MAP remains below goal despite the use of Norepinephrine plus vasopressin

Can also consider Epinephrine for adults with septic shock and signs of cardiac dysfunction with persistent hypotension despite adequate fluid resuscitation

Stimulates alpha, beta 1 and beta 2 (Beta>Alpha)

Phenylephrine

Neo synephrine

Pure alpha agonist

Limit use to tachyarrhythmias, severe aortic stenosis and ventricular outflow obstruction

Comparison of Heart Rate After Phenylephrine vs Norepinephrine Initiation in Patients With Septic Shock and Atrial Fibrillation

- Retrospective review, CHEST, 2022
- 1847 patients with sepsis and atrial fibrillation, 946 norepinephrine, 901 phenylephrine
- In patients with sepsis and AF, the initiation of phenylephrine was associated with modestly lower heart rate compared with norepinephrine
- Heart rate at vasopressor initiation appeared to be an important effect modifier
- Whether modest reductions in heart rate are associated with clinical outcomes requires further study

Angiotensin II

Giapreza

Vasoactive agent

Naturally occurring peptide hormone of the renin-angiotensin-aldosterone system (RASS) that causes vasoconstriction and increases aldosterone release, which then raises blood pressure.

Angiotensin II for the Treatment of Vasodilatory Shock (Athos III Trial)

- Multi center, RCT, published in 2017 NEJM (344 patients, 164 received angiotensin II)
- Compared the addition of angiotensin II or placebo to the addition of norepinephrine (>0.2 mcg/kg/min) or another vasopressor in patient's with vasodilatory shock (did not limit to sepsis)
- Primary endpoint was a response with MAP > 75 or an increase of baseline SBP of > 10 mm Hg at hour three of infusion, without an increase of background vasopressors.
- Many limitations including small sample size, unable to ascertain mortality benefit, follow up only to 28 days

Angiotensin II Infusion for Shock
A Multicenter Study of Postmarketing Use

- A multicenter, retrospective study, 2021, published in CHEST
- 270 patients
- The primary end point of hemodynamic responsiveness to angiotensin II was defined as attainment of mean arterial pressure (MAP) of > 65 mm Hg with a stable or reduced total vasopressor dosage 3 h after drug initiation
- For vasopressor-refractory shock, more than two-thirds of recipients demonstrated a rapid hemodynamic response to angiotensin II that was associated with improved survival
- May have risk of being prothrombotic
- Currently not recommended for use in the Surviving Sepsis guidelines

Surviving Sepsis, 2021 Hemodynamic Management Guidelines

- For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we suggest either adding dobutamine to norepinephrine or using epinephrine alone
- For adults with septic shock, we suggest invasive monitoring of arterial blood pressure over noninvasive monitoring, as soon as practical and if resources are available

Dobutamine

Adrenergic Agonist Agent; Inotrope

Beta >> Alpha

If cardiac dysfunction is present with persistent hypoperfusion, despite adequate volume resuscitation and blood pressure, consider adding Dobutamine or switching to Epinephrine. (Surviving Sepsis, 2021).

Can be given via peripheral IV

May cause tachyarrhythmias

Milrinone

Inotrope; Phosphodiesterase-3 Enzyme Inhibitor

Use is for acute decompensated heart failure

Currently not recommended in septic shock

Epinephrine, dobutamine are preferred

Risk of arrhythmias and hypotension

The Effect of Dobutamine vs Milrinone in Sepsis: A Big Data, Real-World Study

- Retrospective chart review 235 patients with sepsis (183 Dobutamine and 53 with Milrinone)
- For the primary outcome of hospital mortality, there was no significant between-group difference
- Compared with dobutamine, the use of milrinone did not decrease hospital mortality in patients with sepsis. Furthermore, milrinone was associated with more RRT therapy, longer length of ICU stay and hospital stay than dobutamine.

Peripheral Vasopressor Administration

Surviving Sepsis, 2021 Hemodynamic Management Guidelines

- For adults with septic shock, we suggest starting vasopressors peripherally to restore mean arterial pressure rather than delaying initiation until a central venous access is secured

Adverse Events Associated with Administration of Vasopressor Medications through a Peripheral Intravenous Catheter

- Journal of Critical Care, 2021. A Systematic Review and Meta Analysis
- 23 studies, 16,055 patients
- Found the incidence of adverse events is low and all were mild with no episodes of limb ischemia or tissue necrosis.
- No study published to date has directly compared vasopressor administration via PIV to CVC within relation to adverse events
- Known complications of CVC include thrombosis, pneumothorax and CLABSI

Steroids in Septic Shock

Surviving Sepsis, 2021 Additional Therapies Guidelines

- For adults with septic shock and an ongoing requirement for vasopressor therapy we suggest using IV corticosteroids

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (Adrenal Trial)

- International, multicenter, double blind, RCT
- NEJM, 2018, 3800 patients
- Purpose was to evaluate if hydrocortisone (200 mg/day) reduced mortality in patients with septic shock undergoing mechanical ventilation
- Among patients with septic shock undergoing mechanical ventilation, a continuous infusion of hydrocortisone did not result in lower 90-day mortality than placebo
- The time to discharge from the ICU was shorter in the hydrocortisone group than in the placebo group
- The time to the resolution of shock was shorter in the hydrocortisone group than in the placebo group
- Lower incidence of blood transfusion among patients who received hydrocortisone than among those who received placebo
- Hyperglycemia and hypernatremia were more common in the steroid group versus placebo

Hydrocortisone Plus Fludrocortisone for Adults With Septic Shock (APROCCHSS trial)

- Advanced Protein C and Corticosteroids for Human Septic Shock
- Multicenter, double blind RCT, published 2018 NEJM
- 1241 patients
- Compared the response of hydrocortisone plus fludrocortisone, activated drotrecogin alfa, the combination of the three groups or placebos.
- In this trial involving patients with septic shock, 90-day all-cause mortality was lower among patients who received hydrocortisone plus fludrocortisone than among patient's who received placebo
- Higher rates of hyperglycemia in the steroid group.
- No significant difference in gastrointestinal bleeding or infection between the groups

Intravenous Fluids in Septic Shock

Surviving Sepsis, 2021 Hemodynamic Management Guidelines

- For adults with sepsis or septic shock, we recommend using crystalloids as first-line fluid for resuscitation
- There is insufficient evidence to make a recommendation on the use of restrictive versus liberal fluid strategies in the first 24 hr of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after the initial resuscitation

Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension (Clovers trial)

- Unblinded, RCT, superiority trial conducted at 60 U.S. centers
- NEJM, 2023
- 1563 patients (782 restrictive versus 781 liberal)
- Among patients with sepsis-induced hypotension, the restrictive fluid strategy that was used in this trial did not result in significantly lower (or higher) mortality before discharge home by day 90 than the liberal fluid strategy

Restriction of Intravenous Fluid in ICU Patients with Septic Shock (Classic trial)

- International, multcenter, RCT
- Published 2022, NEJM
- 1554 patients (770 restrictive versus 784 standard fluid group)
- Among adult patients with septic shock in the ICU, intravenous fluid restriction did not result in fewer deaths at 90 days than standard intravenous fluid therapy

Surviving Sepsis, 2021 Hemodynamic Management Guidelines

- For adults with sepsis or septic shock, we suggest using balanced crystalloids instead of normal saline for resuscitation

Balanced Crystalloids Versus Saline in Non-Critically Ill Adults (SALT-Ed Trial)

- A single-center, pragmatic, multiple-crossover trial of 13,347 patients
- Comparing balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A) with saline among adults who were treated with intravenous crystalloids in the emergency department and were subsequently hospitalized outside an ICU
- 2018, NEJM
- Among noncritically ill adults treated with intravenous fluids in the emergency department, there was no difference in hospital-free days between treatment with balanced crystalloids and treatment with saline

Balanced Crystalloids versus Saline in Critically Ill Adults (SMART Trial)

- Multicenter, cluster randomized, multiple crossover trial
- 15,802 adults randomized to either receive saline (0.9% sodium chloride) or balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A)
- NEJM, 2018
- Among critically ill adults, the use of balanced crystalloids for intravenous fluid administration resulted in a lower rate of the composite outcome of death from any cause, new renal-replacement therapy, or persistent renal dysfunction than the use of saline

Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9% Saline Solution on Mortality in Critically Ill Patients (BaSICS Trial)

- Multi center, international, double blind RCT
- 10,520 patients after randomization
- To determine the effect of a balanced solution vs saline solution (0.9% sodium chloride) on 90-day survival in critically ill patients
- The primary outcome was 90-day survival
- Among critically ill patients requiring fluid challenges, use of a balanced solution compared with 0.9% saline solution did not significantly reduce 90-day mortality
- Also, no difference in rates of kidney injury
- Study allowed patients with any fluid type given prior to enrollment in the trial

Balanced Multielectrolyte Solution versus Saline in Critically Ill Adults (PLUS Trial)

- Multicenter, RCT, double blind
- NEJM, 2022
- 5037 patients randomized to either receive (Plasma-Lyte 148) or saline as fluid therapy in the intensive care unit (ICU)
- The trial found no evidence that the risk of death or acute kidney injury among critically ill adults in the ICU was lower with the use of balanced crystalloids than with saline

Albumin in Septic Shock

Surviving Sepsis, 2021 Hemodynamic Management Guidelines

- For adults with sepsis or septic shock, we suggest using albumin in patients who received large volumes of crystalloids

A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit (SAFE Trial)

- A multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU
- NEJM, 2004
- 4% albumin versus NSS
- 6997 patients
- The primary outcome measure was death from any cause during the 28-day period after randomization
- In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days
- In the severe sepsis subgroup, a non-significant trend towards lower all cause mortality at 28 days with the albumin group was identified

Albumin Replacement in Patients with Severe Sepsis or Septic Shock (ALBIOS Trial)

- Multicenter, open label, RCT
- NEJM, 2014
- Total of 1818 patients with severe sepsis were randomly assigned to receive 20% albumin and crystalloid solution (910 patients) or crystalloid solution alone (908) for fluid replacement
- The primary outcome measure was death from any cause at 28 days after randomization
- In patients with severe sepsis, albumin replacement in addition to crystalloids, as compared with crystalloids alone, did not improve the rate of survival at 28 and 90 days

Any Questions??

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